REMARKS

Claims 15-25 are canceled. Claims 1 and 12 have been amended. The amendments are supported throughout the application, e.g., at page 27, line 15, and by the examples. Upon entry of this amendment, claims 1-14 and 26-32 will be pending.

Applicants thank the Examiner for his time and helpful discussion during the telephonic interview conducted with the undersigned and his associate on October 9, 2003. The substance of the interview is detailed below according to MPEP §713.04.

Sequence Listing

The Examiner maintains that a sequence listing is needed for the sequence X-Arg-X-X-Arg wherein X is any amino acid. According to the most recent version of 37 C.F.R. §1.821, "Sequences with fewer than four specifically defined nucleotides or amino acids are specifically excluded from this section. 'Specifically defined' means those amino acids other than 'Xaa' and those nucleotide bases other than 'n'." As the X-Arg-X-X-Arg sequence has only two specifically defined amino acids, a sequence listing is not required.

Nonstatutory double patenting rejection

Claims 1-15 are provisionally rejected as unpatentable over the claim of co-pending application 09/407,605 (which is the parent of the instant application and commonly owned). Applicants will remove and obviate the rejection by submitting a terminal disclaimer. A terminal disclaimer is not an admission or comment regarding the merits of the rejection. (Quad Environmental Technologies Corp. v. Union Sanitary District, 946 F.2d 870, 20 USPQ2d 1392 (Fed. Cir. 1991)).

Rejections Under 35 U.S.C. § 103

Claims 1-15 and 26-32 are rejected as unpatentable over Seed WO96/09378 (Seed) in view of Kim et al. 1997, *Gene* 199:293-301 (Kim); Morgan et al., 1987, *Pediatr. Nephrol.* 1:536-539 (Morgan); Bishop et al., 1986, *PNAS USA* 83:4859-63 (Bishop); and Wada et al., 1992,

Nucleic Acids Res. 20:2111-18 (Wada). The rejection has been addressed, in part, by amending the claims. The pending claims are patentable over the cited references for the following reasons, as discussed with the Examiner in the telephonic interview.

The pending claims are limited to a nucleic acid sequence that encodes human α-galactosidase. The Examiner states that the prior art provided a motivation to change non-preferred codons to human preferred codons. However, the passage in Kim cited by the Examiner does not speak to modifying a human sequence, as recited in the claims. Rather, the passage quoted by the Examiner refers to changing non-human sequences (HIV envelope glycoproteins and jellyfish GFP) to match the codons prevalent in human sequences. The passage quoted by the Examines does not teach or suggest any particular level (much less the particularly high level recited in the claims) of human prevalent codons.

Applicants admit that the Examiner presented a proper *prima facie* case of obviousness. However, Applicants submit that the *prima facie* case can be rebutted because Seed and Kim teach away from the invention. Seed teaches "[in] constructing the synthetic genes of the invention it may be desirable to avoid CpG sequences as these sequences may cause gene silencing" (emphasis added), thereby cautioning against and leading away from substantial increased use of CpG pairs, as acknowledged by the Examiner at page 2 of the Office Action. The Examiner, however, is not convinced that Seed teaches away because "Seed did not consider it fatal in reengineering any gene." However, the law does not require that a teaching away be "fatal." The Federal Circuit has said:

> **A prima facie case of obviousness can be rebutted if the applicant...can show "that the art in *any* material respect taught away" from the claimed invention."** [emphasis added; string citation omitted]. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference . . . would be led in a direction divergent from the path that was taken by the applicant" [string citation omitted]. *In re Haruna*, 249 F.3d 1327 (Fed. Cir. 2000)

Therefore, even though a prima facie case of obviousness was made by the Examiner, Applicants showing of a teaching away by Seed (and Kim, as discussed in the reply filed on March 5, 2003) should be sufficient to rebut the rejection.

Further, Applicants note that the Examiner's statements that "the human species has not vanished because of its preference for codons having the CG pairs" supports patentability of the

pending claims. Applicants agree that native human sequences perform well. However, the native human α-galactosidase sequence has a much lower level of human preferred codons than the synthetic sequence recited in the claims. Thus, the optimized functionality of the native human sequence, to which the Examiner refers, relies on codon usage much different than the claimed invention. That is, the claims require a much higher level of human common codons than the native α-galactosidase sequence, which Applicants agree works well in nature. Surprisingly, Applicants found that synthetic α-galactosidase sequences containing the much larger continuous stretches or overall very high numbers of common codons recited in the claims, resulted in 2.0- and 5.7-fold increases in mean α-galactosidase expression compared to the wild-type sequence (see table 10 and accompanying discussion at page 72 of Applicants' disclosure). These are surprising results, especially in view of the teaching away by Seed and Kim. These surprising results also serve to rebut the *prima facie* case of obviousness.

In view of the foregoing, Applicants respectfully request that the rejection be withdrawn.

Enclosed is a Petition for Extension of Time along with the required fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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